Radiotherapy and Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Prospective data registration and clinical trials for particle therapy in Europe

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ARTICLE INFO

Article history:
Received 6 March 2018
Received in revised form 18 May 2018
Accepted 1 June 2018
Available online xxxx

Keywords:
Proton therapy
Prospective data registry
Particle therapy
Model-based approach

ABSTRACT

The overarching aim of work package 1 of the European Proton Therapy Network (EPTN) is to create a firm basis for evidence-based particle therapy at the European level. To achieve this, this work package will set up a worldwide unique prospective data registration programme for nine different tumour sites. Such programme will provide more insights into the current practice across all European particle therapy centres and into the results of particle therapy with regard to radiation-induced toxicity and efficacy in terms of local control and survival.

More importantly, prospective data registration provides major opportunities to continuously improve the quality of particle therapy, by defining bench marks, to identify best practices that may learn others to improve quality of particle therapy, to synchronize selection criteria and to create more homogeneous patient cohorts to evaluate results, which is particularly important in rare tumours.

This will be supported by EORTC through existing and new IT-infrastructure for data collection in different formats next to QA-platforms.

In addition, work package 1 will define the requirements for high quality clinical trials in order to enhance high quality clinical trial proposals and determine alternative methods for RCT, such as the model-based approach.

Particle therapy offers great opportunities to further broaden the therapeutic ratio of radiotherapy by either decreasing the dose to normal tissues while the target dose remains equivalent or by target dose escalation without further excess dose to the normal tissues. However, there is widespread discussion regarding lack of evidence for proton treatment for a wide range of indications. Even for the most widely accepted conditions, paediatric tumours, issues remain as to whether superiority of protons over photons has sufficiently been shown [1]. Reducing dose to normal tissues and organs outside of target areas evidently is the key feature of protons versus photons, but translation of these reductions into clinically relevant benefits has still not been demonstrated consistently, including biological issues such as variable relative biological effectiveness [2].

Therefore, to enhance evidence-based particle therapy, EPTN decided to establish a dedicated work package (work package 1) to create a firm basis for evidence-based particle therapy at a European level. To this purpose, the following objectives were defined:

1. to determine the content of uniform prospective data registration programmes at a European level for the most common tumour types treated with particle therapy;
2. to setup an IT infrastructure that can support the model-based approach at a European level by harmonizing data acquisition, making data Findable, Accessible, Interoperable and Reusable (FAIR) and linking data from different sources and centres [9].

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https://doi.org/10.1016/j.radonc.2018.06.001
0167-8140/

3. to identify the methodological issues related to phase I and II studies as well as to RCTs comparing photons with particles and to define general guidelines for the design of clinical trials to overcome these issues; to establish an Expert Committee to advice and support researchers in Europe in the design of clinical trials in particle therapy.

The aim of this paper is to further explore the background of these objectives and to briefly discuss the strategy to further enhance evidence-based introduction of particle therapy on a European level.

Prospective data registration

The general idea is to create a firm prospective data registration programme for all patients treated in European particle therapy centres which is considered important for a number of reasons:

First, major differences exist between European proton therapy centres on criteria for patient selection, resulting in major heterogeneity of patient populations and eventual outcome. Prospective data collection of all patients treated with proton therapy in Europe will provide essential information on patient mix and outcome and may serve as a basis to discuss and harmonize selection criteria for particle therapy in order to create more homogeneous patient populations. In this way, evaluation of the efficacy of particle therapy in well-defined patient populations can be accelerated, which is particularly useful for relatively rare tumours, such as base of skull tumours and paediatric malignancies. Such data may also be used as to generate hypotheses for and to design future clinical trials.

Second, particle therapy is a relatively new radiation modality and needs to undergo some form of quality assurance. There is major variability in the performance between centres due to differences in delivery and treatment planning equipment, differences in standard operation procedures (e.g. the use of image-guidance and plan adaptation) and differences in expertise, experience, composition and treatment philosophies of the health care teams involved. Multicentre uniform prospective data collection provides unique opportunities to define benchmarks and to identify best practices. This information can be used to continuously improve the quality of particle therapy on a European level.

Third, prospective data collection is the hall mark of the model-based approach, an evidence-based methodology introduced in the Netherlands for both patient selection and clinical validation of proton therapy, which could serve as an alternative for randomized controlled trials (RCTs), which are still considered the gold standard of evidence-based medicine.

In this regard, it should be emphasized that there is no doubt that an RCT is the most appropriate study design when the main goal is to increase treatment efficacy in terms of local control or survival by target dose escalation beyond the dose considered current standard. For such an application of particles, not only the effect of dose escalation on tumour control must be explored, but also the risks of consequent dose escalation to the normal tissues nearby the target beyond levels that are normally administered. In addition, when the biological effect of particles is possibly different from currently used photons, e.g. higher RBE when using carbon ions, RCTs are required not only when the primary objective is to improve local control, but also when particles are applied to reduce radiation-induced side effects.

It is expected that in most cases, protons will be applied to prevent radiation-induced side effects and/or induction of secondary tumours. In 2009, the Dutch Health Council produced an extensive report on the expected indications for proton therapy and concluded that around 5–10% of all patients currently treated with radiotherapy would benefit from protons, and that most (85%) of them will be treated with particles to prevent radiation-induced side effects and/or secondary tumour induction [3]. For the validation of radiation technologies primarily aiming at reduction of side effects, there is a growing awareness that equating evidence-based medicine with RCTs is an undue simplification and that other methodologies, such as the model-based approach, are available and need further exploitation [3,4].

Irrespective of the research question, the design of RCTs when comparing two different radiation technologies may be subject to methodological difficulties and pitfalls as well. Therefore, it is important not only to identify and address these difficulties but also to define how they can be prevented. In addition, the definition of minimal requirements for the design of RCTs comparing photons with particles is desperately needed to guarantee generalizability of results and eventual proper translation into routine clinical practice.

In the Netherlands, an alternative methodology has been developed to select patients for proton therapy and to validate the benefit of protons over photons: the so-called model-based approach (MBA). The MBA is an evidence-based methodology designed to yield evidence for a more rational selection of patients who would most likely derive clinically relevant benefits from particle therapy in terms of prevention of radiation-induced side effects [5,6]. The rationale behind model-based selection is that particle therapy will only lead to broaden the therapeutic window by decreasing toxicity, when three essential requirements are met: (1) the dose to the target is equivalent to photons and considered current standard; (2) normal tissue sparing can be obtained with particles compared to photons (ΔDose), and (3) ΔDose results in a clinically significant lower complication risk (or else lower normal tissue complication probability (ΔNTCP)). It should be stressed that transforming dose into complication risk requires multivariable NTCP-models including non-dosimetric features (e.g., patients' age, concomitant chemotherapy) and that therefore a decrease of dose will not always translate into a relevant decrease of complication risks.

The key research agenda for the near future should therefore be to validate this thesis by attempting to falsify the hypothesis that NTCP reduction leads to less toxicity, which is the main principle of model-based validation. In addition, it is very likely that NTCP-models need continuous updating and adjustments due to differences in patient mix and technological evolvements [7,8]. For this purpose, uniform prospective data registration at a European level of all patients treated with proton therapy is essential.

Our main priority is therefore to establish uniform prospective data registration programmes on a European level for the most common tumour types treated with particle therapy. Therefore, nine tumour-specific sub-tasks were established for patient groups that are frequently treated with particle therapy, including tumours of the central nervous system (CNS), head and neck, breast, lung, oesophagus, lymphoma, sarcoma, prostate, and paediatric cancer. Next to a generic assessment that applies for all patients irrespective of tumour site, these sub-tasks are defining the data sets for each tumour site.

As mentioned earlier, the main objective of the prospective data registry is to get more information on the characteristics of patients treated with particles and to get more insight into the most relevant outcome measures. There is consensus that such registry can only be informative and successful when in principle all European particle centres will be able to participate and when patient accrual and compliance to the programme is high. However, reality is that resources for data registries are generally limited. Therefore, EPTN decided to define different levels of data registries to on the one hand ensure participation of all centres and, at the other hand, offer opportunities to collect more comprehensive or detailed data by a limited number of centres (Table 1).

Please cite this article in press as: Langendijk JA et al. Prospective data registration and clinical trials for particle therapy in Europe. Radiother Oncol (2018), https://doi.org/10.1016/j.radonc.2018.06.001